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Review

Effect of liver fibrotic changes on testicular histological structure: An updated review

Liver fibrosis and structural testicular affection

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Abstract

The liver plays a crucial role in maintaining adequate endocrine homeostasis including the endocrine function of the testis. Testicular atrophy and gonadal dysfunction have been clinically reported in advanced cirrhotic liver diseases. This study was conducted to review the effect of liver fibrotic changes induced by different agents on the structure of testis and the mechanisms underlying these effects. Chemical-induced liver fibrosis was found to have a negative impact on testicular structures. Carbon tetrachloride (CCl_4) was frequently described to increase apoptosis of spermatogenic cells and reduced testicular transferrin expression through enhancing lipid peroxidation or direct toxic effect on the testis. Thioacetamide, another hepatotoxin, was reported to have harmful effects on sperm structure and function. Deltamethrin had hepatic changes that were associated with marked degeneration in rat seminiferous tubules. Cyclosporine A, an immunosuppressive drug, induced Sertoli and germ cell vacuolation besides inducing hepatic cytotoxicity. Testes of rats which chronically received alcohol, showed hypocellularity of the seminiferous tubules, degeneration of germinal epithelial and interstitial cells along with reduced sperm count and motility which was attributed to changes in the structure of the mitochondria. Portasystemic shunting and portal hypertension in rats were associated with reduced volume of germinal epithelium, reduced cell birth, reduced or complete loss of spermatogenic activity and marked increase in apoptosis. Virus-induced chronic active hepatitis was associated with sperm damage and reduced sperm quality parameters.

Conclusion: Hepatic fibrotic changes induced by different injurious stimuli were found to have a harmful impact on testicular structure and function.

Keywords

Liver Fibrosis; Testis; Spermatogenesis; CCl_4; Hepatotoxic; Sertoli; Testosterone; Infertility

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Introduction

The liver plays a crucial role in the synthesis and metabolism of hormones, the synthesis of enzymes and cytokines which are all important in maintaining sufficient endocrine homeostasis. Gonadal integrity depends on a normal liver function [1]. The liver affects the endocrine function of the testis through numerous mechanisms as it possesses a vital role in maintaining the levels of free testosterone. It also affects the endocrine homeostasis of the sex hormones by transforming androgens into estrogens and the inactivation of the sex hormones by specific enzymes [2].

Liver diseases became prevalence worldwide. It was described that the main etiologies of liver disease were nonalcoholic fatty liver disease and alcoholic liver disease. The independent predictors of increased liver stiffness included abdominal obesity, type 2 diabetes, and elevated levels triglycerides. Subjects with no risk factors had only a 0.4% prevalence of significant liver fibrosis (liver stiffness ≥9.2 kPa), compared with 5% in those with at least one risk factor from the listed risk factors [3].

Testicular spermatogenesis is a sophisticated and complex differentiation process. It comprises an accurately programmed and coordinated production of many generations of germ cells via division of spermatogonia (proliferative phase) and meiotic phase; (spermiogenic phase) [4]. Sertoli cells support and help to move the germ cells towards the lumen of the tubules. In addition, these cells help the transmission of the important molecules to the germ cells [5] (Figure 1).

Leydig cells in the interstitium of the testes secret testosterone which is synthesized under the control of the "negative feedback to the anterior pituitary gland". The latter releases luteinizing hormone (LH) which in turn is regulated by gonadotropin-releasing hormone (GnRH) of the hypothalamus [6]. In order to have a successful germ cell development, a balance between hormones secreted by the hypothalamus, pituitary gland, and the testis should be existed [7] (Figure 2).

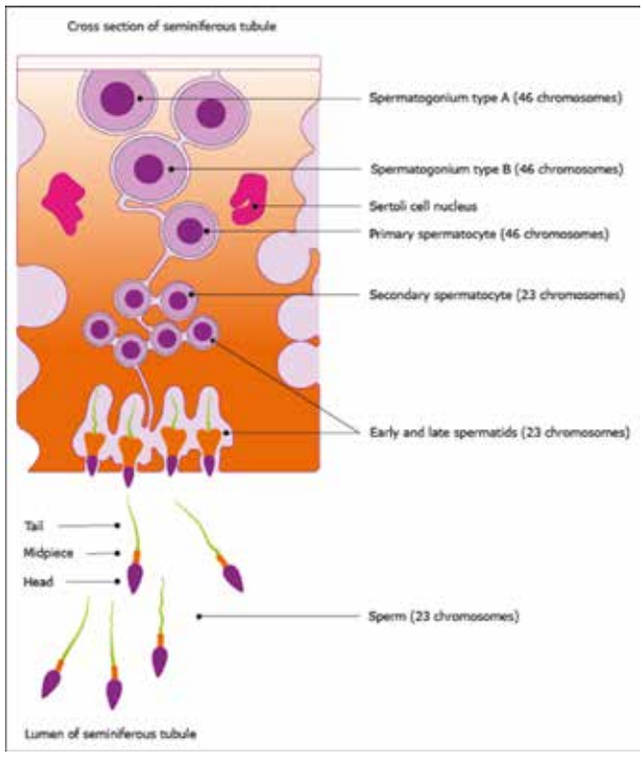

Figure 1. A schematic figure representing the cross-section of a seminiferous tubule illustrating the stepwise process of spermatogenesis. Initially, immature cells (spermatogonia) located close to the basal membrane divide by several rounds of mitosis into primary and secondary spermatocytes that divide by meiosis to form spermatids. The final step of spermatogenesis takes place in the lumen of the seminiferous tubule where spermatids differentiate into haploid sperm cells. Cited after obtaining permission from Uhlén et al. [40].

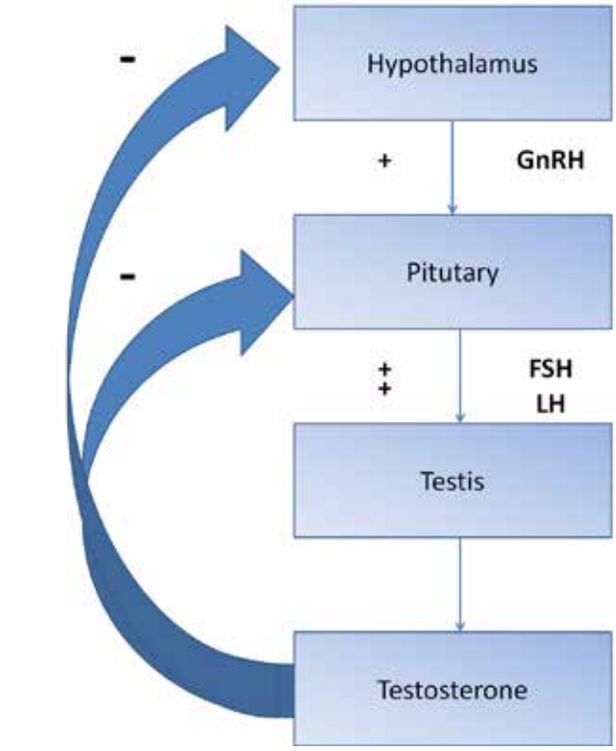

Figure 2. Hypothalamic-pituitary-testicular axis

Testicular atrophy and gonadal dysfunction have been clinically reported in advanced cirrhotic liver diseases [8, 9]. The structural alternations of testes in alcoholic and nonalcoholic liver disease in humans have been reported in many studies [10]. This study was conducted to review the effect of liver fibrosis induced by different agents on the structure of testis and the mechanisms underlying these effects.

Chemically-induced liver fibrosis

Spermatogonial degeneration could occur as a result of exposure to toxic chemicals [11]. Carbon tetrachloride [CCl_4] is a hepatotoxin substance when administered, it results in steatosis, necrosis, and cirrhosis in animals [12]. It initiates oxidative stress with subsequent development of lipid peroxidation in cell membranes [13]. Changes in the spermatogenic cycle, the disintegration of the seminiferous tubules as well as hypogonadism have been produced in rats received CCl_4 [14].

In a previous study on Wistar rats with advanced ascitic cirrhosis induced by CCl_4 confirmed by deterioration of liver function tests, the weight and size of the testis were reduced. These rats showed significantly low serum testosterone and significantly high serum LH when compared to the control rats. Histopathological examination of the testis of these rats revealed a decrease in tubular diameters, appearance of aberrant cells in tubular lumen, disappearance of the germinal line, and decreased cell division and spermatogenesis as well as testicular transferrin expression [15]. In their study, administration of

insulin-like growth factor-1 (IGF-I) resulted in the restoration of the size and weight of the testis as well as improvement of all histopathological abnormalities and serum levels of sex hormones [16] (Figure 3). Rappaport and Smith reported that IGF-1 enhances testosterone formation and spermatogenesis and its decrease could result in the development of hypogonadism associated with cirrhosis [17].

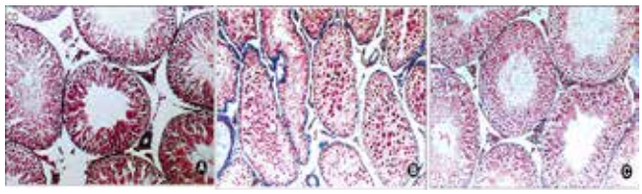

Figure 3. Testicular histological section of normal rat (CO) demonstrating active spermatogenesis in normal-size seminiferous tubules. Seminiferous tubules in testes from untreated cirrhotic animals (CI) appear seriously damaged. These animals show a decrease of tubular diameter, vacuolization on the germinal epithelium, loss of germinal line, total or partial reduction of spermatogenesis, the presence of abnormal spermatids, and increased collagen deposition (arrow) (Masson's stain; original magnification 3150). Cirrhotic rats treated with IGF-I [CI IGF] show reversal of all these alterations. Cited after obtaining permission from Castilla-Cortázar et al. [14].

The histopathological changes described in the testis of rats suffering from liver cirrhosis resemble those reported in alcoholic cirrhosis [8] and those reported in chronic testicular ischemia [17]. One of the most important findings reported in the study by Castilla-Cortázar et al. on cirrhotic rats was the reduced Sertoli cells expression of transferrin [18]. Testicular transferrin expression is considered a reliable marker of the hematotesticular barrier integrity [19]. Castilla-Cortázar et al. proposed that the initial phase of the pathogenesis of testicular atrophy occurred in advanced cirrhosis might be the reduced expression of transferrin, dysfunction of Sertoli cells and consequently the disruption in blood-testis barrier structure [18] (Figure 4). Among the changes reported by Castilla-Cortázar et

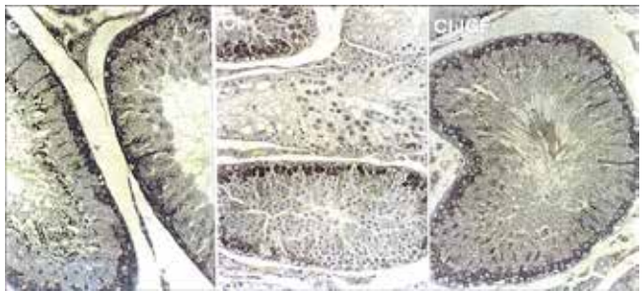

Figure 4. Immunohistochemistry for testicular transferrin in seminiferous tubules. Transferrin immunostaining can be seen at the level of Sertoli cells and in germ cells in normal rats (CO) and in cirrhotic rats treated with IGF-I (CI 1 IGF), but absent transferrin immunostaining is observed in untreated cirrhotic rats (CI). Cited after obtaining permission from Castilla-Cortazar et al. [15]

al. was a significant reduction in testicular cellular proliferation, as evaluated by immunostaining of proliferating cellular nuclear antigen (PCNA) [18] (Figure 5).

Khan and Ahmed previously reported that testes of CCl_4-treated rats showed differences in their histology [20]. Some seminiferous tubules were atrophied while others possessed defined basement membranes but most of the germ cells were degenerated and had deformed sperms. Fibroblast and inflammatory cells partially replaced the ground substance within the interstitium. In this study, CCl_4 induced a significant decrease

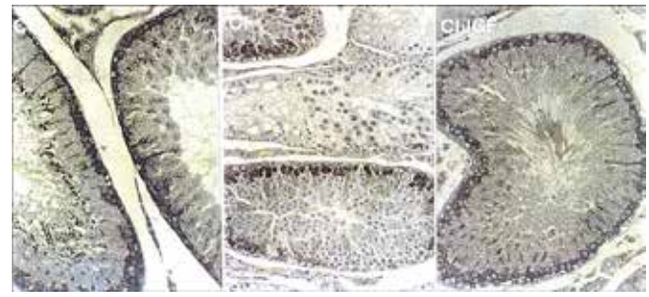

Figure 5. The study of proliferative activity, assessed by PCNA immunostaining. A significant reduction of cellular proliferation was observed in rats with compensated cirrhosis. This reduction was normalized in IGF-1 treated cirrhotic group (CI+IGF). (×200 magnification, in the three pictures). Cited after obtaining permission from Castilla-Cortázar et al. [18]

in the activity of catalase (CAT), Peroxidase (POD), Superoxide dismutase (SOD), and Glutathione peroxidase activity (GSH-Px), in the testis and depleted the GSH contents and enhanced lipid peroxidation. Reduced activity of antioxidant enzymes in the testis and reduced content of GSH turn the CCl_4-induced oxidative stress into the marked condition and the intrinsic mechanism of a body could not relieve the resulted damage. Khan and Ahmed postulated that CCl_4-induced damage in germinal epithelial could enhance spermatogenesis partially due to reduced synthesis of androgen binding proteins [20]. Damage effects of CCl_4 may lead to an inability of the pituitary to secrete follicle stimulating hormone (FSH) and LH and that will result in testicular dysfunction and infertility.

In another study, Al-Olayan et al. reported that CCl_4 induced a significant increase in testes and relative testes weights compared with the control rats [21]. This was attributed to edema and fluid accumulation. They attributed these changes to CCl_4-induced reduction in the activities of antioxidant enzymes included catalase (CAT), Superoxide Dismutase (SOD), Glutathione Peroxidase (GPX), GR and GST which is probably due to protein inactivation by reactive oxygen species (ROS) with subsequent loss of specific protein function [21].

Abdel Moneim added that injections of CCl_4 at the dose of 2 ml/kg body weight (BW) once a week for 12 weeks induced degeneration of germ and Leydig cells along with deformities in spermatogenesis [22]. In addition, CCl_4 up-regulated caspase-3 expression in the testes of rats. This pointed to that the cell death mechanism involved caspase-3 activation. Degeneration of the testes and consequent oxidative stress-activated caspase-3 increased cell death.

It has been stated that CCl_4 might have a direct toxic action on the testicular tissue and is possibly weaken gonadal effect to FSH and LH and reduced synthesis of testosterone. In addition, liver diseases in humans occur in many hormone disorders, including reduced serum levels of cortisol, testosterone, FSH, and insulin and increased prolactin concentrations in males [23].

Thioacetamide (TAA) is another hepatotoxin which causes liver cirrhosis, oxidative stress, and reduced catalase and glutathione peroxidase [24] (Figure 6). Di[2-ethylhexyl]phthalate (DEHP) and Di[2-ethylhexyl]adipate (DEHA) are principal phthalates utilized in a variety of products including medical devices, cabling, flooring, and interiors. DEHA can be found in many consumer items such as bath oils, eye shadow and cosmetic foundations [25]. Testes of rats received TAA (at a dose of 200 mg/kg intra-

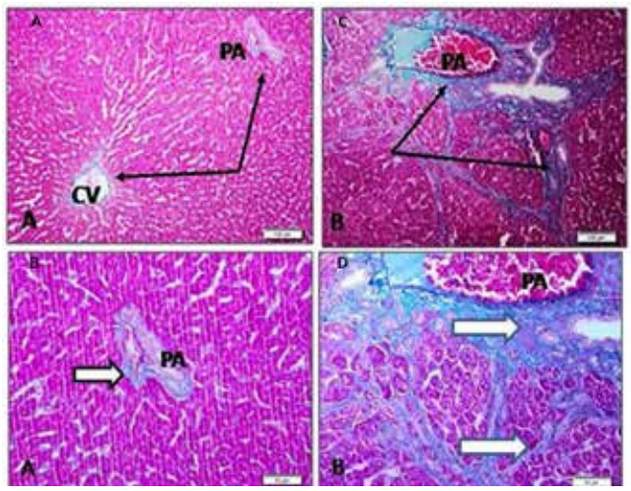

Figure 6. Sections of rat liver stained with Masson's trichrome in (A, B) normal control group showing normal collagen distribution around the central vein (CV) and portal area (PA). (C, D) Thioacetamide group shows marked collagen deposition in the portal area (PA) and fibrous bridging between lobules (black arrows) (Masson Trichrome stain x200, 600). Cited after obtaining permission from Murad et al. [41].

peritoneal, 3 times/week for 4 weeks) followed by DEHP for 4 weeks showed severe atrophy of seminiferous tubules and loss of spermatogenic cells while some tubules completely lost spermatogenesis and had empty lumina. On the other hand, rats received DEHP alone showed the lesser extent of seminiferous tubules atrophy and tubular degeneration in testes. Abul et al. found a drastic decrease in the level of antioxidant enzymes in the testes of thioacetamide-induced cirrhotic rats which proposed to have harmful effects on sperm function. These reported changes were attributed to anti-proliferative impact on Sertoli cells and reducing testosterone synthesis [26].

Deltamethrin, a synthetic pyrethroid insecticide used worldwide in agriculture household pest control, has a deleterious effect of on both liver and reproductive system [27]. Deltamethrin induced notable histopathological hepatic changes including necrosis and mononuclear cells infiltration around the central vein as well as hepatocytes vacuolization [27]. In addition to these hepatic changes, deltamethrin induced marked degeneration in rat seminiferous tubules evident by lost shape and outline of the tubules as well as the absence of germ cells. Multiple hemorrhages and degeneration of the intertubular tissue were among the deltamethrin-induced changes in the testis.

Cyclosporine A has many biological actions included anti-inflammatory and immunosuppressive effects. On the other hand, it has definite adverse side effects, including hepatic cytotoxicity [28]. It was reported that "cyclosporine A administered to rats at a dose of 15 mg/kg per day for 56 days by gavage, increased testicular connective tissue volumetric proportion and reduced Leydig cell volumetric proportion. The majority of the Leydig cells of rats treated with cyclosporine A appeared smaller in size and their shapes were elongated and sometimes irregular. When examined using the transmission electron microscopy (TEM), testis of cyclosporine A-treated rats showed Sertoli cells with many cytoplasmic vacuoles and lipid droplets. Some germ cells were degenerated with vacuoles mostly arising from the endoplasmic reticulum. Round spermatids with nuclear protrusions were seen. The late spermatids appeared deformed with irregular acrosomes. Late spermatids with random orientation were also observed in the basal and luminal parts of the seminiferous epithelium [28].

Alcohol-induced liver fibrosis:

Alcohol-induced cirrhosis is commonly associated with gonadal dysfunction as reported by Van Thiel et al. [29]. In patients suffering from such condition, the level of hypogonadism has been related to the degree of liver affection [29]. Testes of sexually mature male Sprague–Dawley rats received alcohol orally at 7 ml/kg BW three times in a week for 8 weeks showed atrophy and significant reductions in the diameter of the seminiferous tubules and hypocellularity of the spermatogenic cells. Sperm count and motility were also significantly reduced in rats received alcohol. Assessment of hormonal profile showed a significant decrease in testosterone level while LH and FSH remained unchanged. Recovery from these changes was observed as the testosterone level increased especifically on the seminiferous epithelium [30] (Figure 7).

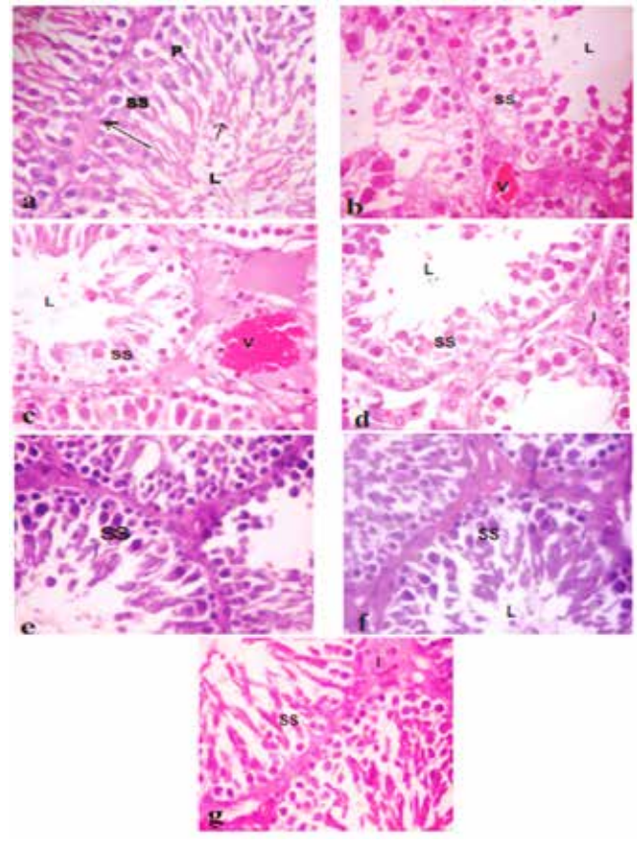

Figure 7. [a] Cross-Section of the testis of control rat (b–d) Cross-Section of the testis of rat treated with alcohol for two, four, and eight weeks respectively showing hypocellularity, reduction in cells of the spermatogenic series (SS). (e–g) Cross-Section of the testes of rat treated with alcohol for two, four and eight weeks respectively followed by the same corresponding number of weeks for recovery showing a slight reduction in the cells of the spermatogenic series (SS) (H & E X400). Cited after obtaining permission from Dosumu et al. [30].

Dosumu previously reported that ethanol changes the structure of the mitochondria of the testicular cells with subsequent compromise in testicular energy metabolism [31]. A large number of nonmotile/dead spermatozoa observed in chronic ethanol consumption in the rat was attributed to the compromised structure of the spermatozoa via the mitochondrial pathway [30]. Ethanol causes a reduction in the ability of the mitochondria to

facilitate protein synthesis due to alterations in mitochondrial ribosomes which makes them less functional with subsequent stimulation of both apoptotic and necrotic cell death. The latter contribute to the development of alcohol-induced testicular injury evidenced by sloughing and degeneration of germinal epithelium and interstitial cells [32]. Regarding the mechanism by which alcohol affects testis, some studies revealed that alcohol affects directly the testicular tissue [33], while others noted that alcohol affects the Hypothalamic-Pituitary-Gonadal axis [34, 35].

Other types of liver fibrosis:

Portal-systemic shunting that resulted from the intrinsic liver disease might be behind in part for gonadal atrophy associated with advanced liver disease [36]. During their study on the effect of portosystemic shunting and portal hypertension on the testis of rats, Van Thiel et al. reported that the weight of the testes was markedly reduced in rats which underwent portocaval shunting (PCS) (reached 42% of the control value) [36]. They proposed that PCS is primarily responsible for the gonadal damage. They added that a minimal reduction in testicular weight was recorded in rats with portal hypertension from partial portal vein ligation.

In a later study conducted by Zaitoun et al. the testicular histological changes induced by portosystemic shunting were assessed using a quantitative stereology technique in order to focus on the effect on the germinal epithelium of seminiferous tubules as the chief component of testis [37]. They reported that "the PCS induced four- to six-fold decrease in the volume of germinal epithelium compared to the controls. In addition, PCS induced a reduction in the cell birth (mitosis) with the reduction to complete loss of spermatogenic activity (maturation arrest), sloughing of the germinal epithelial cells, together with a marked increase in apoptosis. The net results are that the tubules become lined by Sertoli cells only, with markedly smaller seminiferous tubules (testicular atrophy). They also reported no marked change in the number of mast cells after PCS, signifying that the mast cells have no role in producing testicular atrophy. Finally, Zaitoun et al. reported that these observed testicular histological changes were attributed to the impact of LH and testosterone hormones on the germinal epithelium [37].

In a patient with chronic hepatitis, the level of gonadal dysfunction was reported to be related to the level of liver damage [38]. Gong et al., concluded that virus-induced chronic active hepatitis enhances oxidative stress in the reproductive system, aggravates sperm damage, and affects sperm quality parameters" [39]. They reported that the total sperm motility and sperm survival rate markedly decreased while the sperm DNA fragmentation index markedly increased in infertile males suffering from chronic viral hepatitis than in the healthy controls and infertile patients. Durazzo et al. reported that, in addition to hypogonadism, the factors disturbing fertility in patients with liver cirrhosis comprise toxic-metabolic injury to the testis and any concomitant hepatitis C virus (HCV) infection, which might decrease the number and motility of the spermatozoa in the semen [40].

In a study aimed to evaluate the effect of hepatitis E virus (HEV) on the testis after experimental infection in Mongolian gerbils showed the presence of HEV in the testis. The histopathological changes shown using the transmission electron microscope revealed the presence of many vacuoles in Sertoli cells, cristae formation in mitochondria, irregularity in the seminiferous tubules, karyolysis, missing nuclei and apoptotic bodies in spermatogonia. They reported that HEV itself does not damage the tissues or site; it is the immune system that results in these histopathological alternations in the infected tissues [41].

In chronic cholestatic liver dysfunction model induced by bile duct ligation in mice and chickens, testes showed many structural changes including tubular distortion and atrophy, associated with thick irregular boundaries, vacuolation, disorganized epithelium, and exfoliated cells [42, 43]. These changes were reported to result from "the detergent-like effect of the toxic bile acids" which is known to enhance membranous lipid polarity and fluidity [44, 45].

Conclusions:

Reviewing of the literature revealed an association between liver fibrosis, resulted from exposure to toxic chemicals, alcohol or other causes, and hypogonadism in both human and experimental animals. This hypogonadism was accompanied by testicular histopathological changes included degeneration and sloughing of spermatogenic cells, apoptosis of germ cells, reduced cell mitosis and increased testicular interstitial fibrosis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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